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FILE 'HCAPLUS' ENTERED AT 11:25:56 ON 01 APR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 1 Apr 2004  VOL 140 ISS 14
FILE LAST UPDATED: 31 Mar 2004  (20040331/ED)

 This file contains CAS Registry Numbers for easy and accurate
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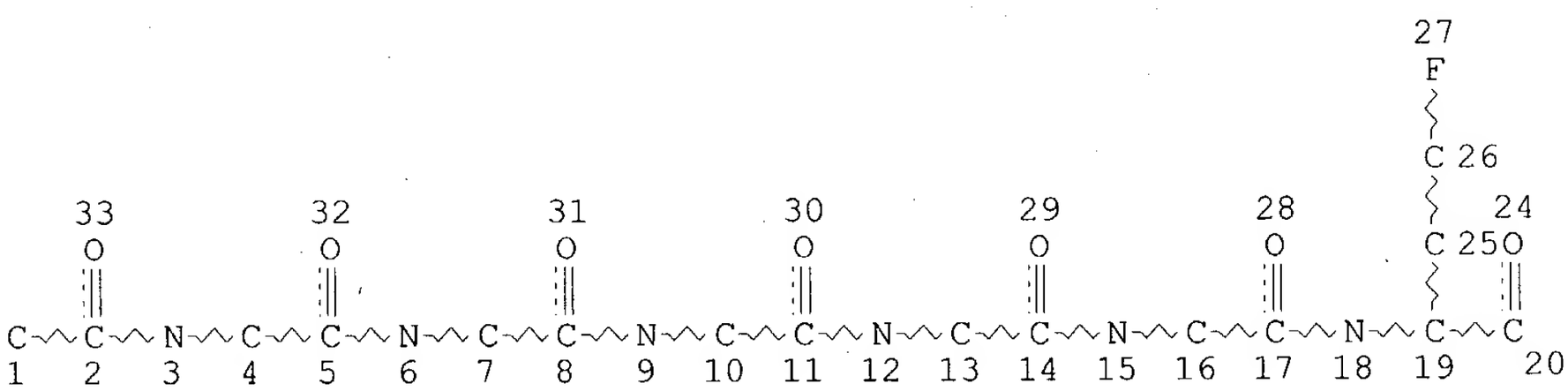


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GRAPH ATTRIBUTES:
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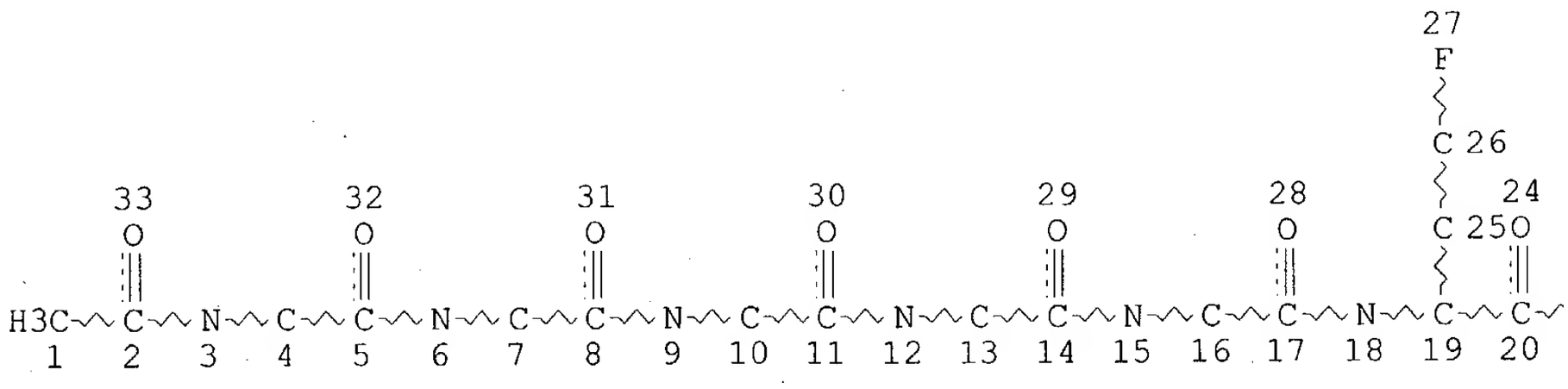

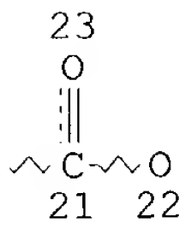

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NUMBER OF NODES IS 33

STEREO ATTRIBUTES: NONE
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L19 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:116982 HCAPLUS
DOCUMENT NUMBER: 137:47425
TITLE: Evolution, synthesis and SAR of tripeptide α-ketoacid inhibitors of the hepatitis C virus NS3/NS4A serine protease
AUTHOR(S): Colarusso, Stefania; Gerlach, Benjamin; Koch, Uwe; Muraglia, Ester; Conte, Immacolata; Stansfield, Ian; Matassa, Victor G.; Narjes, Frank
CORPORATE SOURCE: Department of Chemistry, MRL Rome, IRBM, Rome, Pomezia, 00040, Italy
SOURCE: Bioorganic & Medicinal Chemistry Letters (2002), 12(4), 705-708
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:47425

AB N-Terminal truncation of the hexapeptide ketoacid MeCO-Asp-Glu-NHCH(CHPh2)CO-Glu-NHCH(CH2c-C6H11)CONHCH(CH2CHF2)CO2H (all-L stereochem.) (c-C6H11= cyclohexyl) gave rise to potent tripeptide inhibitors of the hepatitis C virus NS3 protease/NS4A cofactor complex. Optimization of these tripeptides led to ketoacid BOC-NHCH(c-C5H9)CO-Leu-NHCH(CH2CHF2)COCO2H (all-L stereochem.) (BOC = tert-butoxycarbonyl, c-C5H9 = cyclopentyl) with an IC50 of 0.38 μM. The SAR of these tripeptides is discussed in the light of the recently published crystal structures of a ternary tripeptide/NS3/NS4A complexes.

IT **262437-54-7**
RL: PAC (Pharmacological activity); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(preparation and structure-activity relationship of tripeptide ketoacid inhibitors of hepatitis C virus serine protease)

IT **262437-54-7DP,** derivs.
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and structure-activity relationship of tripeptide ketoacid inhibitors of hepatitis C virus serine protease)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:116981 HCAPLUS
DOCUMENT NUMBER: 137:149812
TITLE: A designed P1 cysteine mimetic for covalent and non-covalent inhibitors of HCV NS3 protease
AUTHOR(S): Narjes, Frank; Koehler, Konrad F.; Koch, Uwe; Gerlach, Benjamin; Colarusso, Stefania; Steinkuhler, Christian; Brunetti, Mirko; Altamura, Sergio; De Francesco, Raffaele; Matassa, Victor G.
CORPORATE SOURCE: Department of Chemistry, MRL Rome, IRBM, Rome, Pomezia, 00040, Italy
SOURCE: Bioorganic & Medicinal Chemistry Letters (2002), 12(4), 701-704
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The difluoromethyl group was designed by computational chemical methods as a mimetic of the canonical P1 cysteine thiol for inhibitors of the hepatitis C virus NS3 protease. This modification led to the development of competitive, non-covalent inhibitor AcAspGlu-NHCH(CHPH2)CO-Glu-NHCH(CH2C6H11)CONHCH(CH2CHF2)R (I, R = CHO) Ki 30 nM and reversible covalent inhibitors (I, R = CO2H) Ki 0.5 nM; and (I, R = COCO2H) Ki* 10 pM.
IT **262437-54-7 444990-66-3**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(designed P1 cysteine mimetic for covalent and non-covalent inhibitors of HCV NS3 protease)
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:352482 HCAPLUS
DOCUMENT NUMBER: 133:189820
TITLE: Probing the active site of the hepatitis C virus serine protease by fluorescence resonance energy transfer
AUTHOR(S): Fattori, Daniela; Urbani, Andrea; Brunetti, Mirko; Ingenito, Raffaele; Pessi, Antonello; Prendergast, Kristine; Narjes, Frank; Matassa, Victor G.; De Francesco, Raffaele; Steinkuhler, Christian
CORPORATE SOURCE: Istituto di Ricerche di Biologia Molecolare "P. Angeletti", Rome, 00040, Italy
SOURCE: Journal of Biological Chemistry (2000), 275(20), 15106-15113
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A serine protease domain contained within the viral NS3 protein is a key player in the maturational processing of the hepatitis C virus polyprotein and a prime target for the development of antiviral drugs. In the present work, we describe a dansylated hexapeptide inhibitor of this enzyme. Active site occupancy by this compound could be monitored following fluorescence resonance energy transfer between the dansyl fluorophore and protein tryptophan residues and could be used to (1) unambiguously assess active site binding of NS3 protease inhibitors, (2) directly determine equilibrium and pre-steady-state parameters of enzyme-inhibitor complex formation, and (3) dissect, using site-directed mutagenesis, the contribution of single residues of NS3 to inhibitor binding in direct binding assays. The assay

was also used to characterize the inhibition of the NS3 protease by its cleavage products. We show that enzyme-product inhibitor complex formation depends on the presence of an NS4A cofactor peptide. Equilibrium and pre-steady-state data support an ordered mechanism of ternary (enzyme-inhibitor-cofactor) complex formation, requiring cofactor complexation prior to inhibitor binding.

IT **262437-54-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; probing the active site of the hepatitis C virus NS3 serine proteinase by fluorescence resonance energy transfer)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:68910 HCAPLUS
DOCUMENT NUMBER: 132:245829
TITLE: α-Ketoacids Are Potent Slow Binding Inhibitors of the Hepatitis C Virus NS3 Protease
AUTHOR(S): Narjes, Frank; Brunetti, Mirko; Colarusso, Stefania; Gerlach, Benjamin; Koch, Uwe; Biasiol, Gabriella; Fattori, Daniela; De Francesco, Raffaele; Matassa, Victor G.; Steinkuehler, Christian
CORPORATE SOURCE: Departments of Biochemistry Medicinal Chemistry and Computational Chemistry, Istituto di Ricerche di Biologia Molecolare (IRBM) P. Angeletti, Pomezia, 00040, Italy
SOURCE: Biochemistry (2000), 39(7), 1849-1861
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The replication of the hepatitis C virus (HCV), an important human pathogen, crucially depends on the proteolytic maturation of a large viral polyprotein precursor. The viral nonstructural protein 3 (NS3) harbors a serine protease domain that plays a pivotal role in this process, being responsible for four out of the five cleavage events that occur in the nonstructural region of the HCV polyprotein. We here show that hexapeptide, tetrapeptide, and tripeptide α-ketoacids are potent, slow binding inhibitors of this enzyme. Their mechanism of inhibition involves the rapid formation of a noncovalent collision complex in a diffusion-limited, electrostatically driven association reaction followed by a slow isomerization step resulting in a very tight complex. PH dependence expts. point to the protonated catalytic His 57 as an important determinant for formation of the collision complex. Ki values of the collision complexes vary between 3 nM and 18.5 μM and largely depend on contacts made by the peptide moiety of the inhibitors. Site-directed mutagenesis indicates that Lys 136 selectively participates in stabilization of the tight complex but not of the collision complex. A significant solvent isotope effect on the isomerization rate constant is suggestive of a chemical step being rate limiting for tight complex formation. The potency of these compds. is dominated by their slow dissociation rate consts., leading to complex half-lives of 11-48 h and overall Ki values between 10 pM and 67 nM. The rate consts. describing the formation and the dissociation of the tight complex are relatively independent of the peptide moiety and appear to predominantly reflect the intrinsic chemical reactivity of the ketoacid function.

IT **262437-54-7P 262437-57-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of α-ketoacids as potent slow binding inhibitors of

hepatitis C virus NS3 protease)
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:795834 HCAPLUS
DOCUMENT NUMBER: 132:36034
TITLE: Preparation of peptide inhibitors of hepatitis C virus NS3 protease
INVENTOR(S): Matassa, Victor; Narjes, Frank; Koehler, Konrad; Ontoria, Jesus; Poma, Marco; Marchetti, Antonella
PATENT ASSIGNEE(S): Istituto Di Ricerche Di Biologia Molecolare P Angeletti S.p.A., Italy
SOURCE: PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964442	A1	19991216	WO 1999-GB1824	19990609
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AU 9942798	A1	19991230	AU 1999-42798	19990609
AU 754773	B2	20021121		
EP 1084137	A1	20010321	EP 1999-955475	19990609
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				

PRIORITY APPLN. INFO.: GB 1998-12523 A 19980610
WO 1999-GB1824 W 19990609

AB Fluorinated oligopeptides Y-B-A-X or Y-B-A'-X' [A is an amino acid residue NHCH(CH2CHF2)(CH2)mCO and A' is NHCHR1(CH2)mCO (m = 0, 1; R1 is a fluorine-substituted hydrocarbyl side chain); B is a naturally or non-naturally occurring amino acid residue NHCHR2CO (R2 is a nonpolar or polar but uncharged side chain or is a side chain containing an acidic functionality); X = CO2R8, H, OR8, CF3, CONR9R10, NHSO2R25, or certain 5-membered heterocyclic groups (R8, R9, R10, R25 = H, alkyl, alkenyl, aryl, aralkyl); X' = NHSO2N25; Y = Z-F-E-D-C (C is a natural or non-natural amino acid residue having non-polar, polar but uncharged, or acidic side chains; D, E, and F may be absent or represent a natural or non-natural amino acid; Z is absent, H, or R7CO which forms an amide, urethane, or urea linkage with the nitrogen atom to which it is attached) or R13CO (R13 is an aliphatic or aromatic group containing 1-25 carbon atoms, 0-5 oxygen atoms, 0-3 nitrogen atoms, 0-2 sulfur atoms, and up to 9 other heteroatoms)] were prepared as inhibitors of hepatitis C virus NS3 protease. Thus, Ac-Asp-Glu-Met-Glu-Glu-NHCH(CH2CHF2)CO2H-(S), prepared by coupling of (S)-tert-Bu 2-amino-4,4-difluorobutanoate hydrochloride with protected pentapeptide, showed IC50 for inhibition of NS3 protease.

IT **252355-88-7P 252355-90-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide inhibitors of hepatitis C virus NS3 protease)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file reg
FILE 'REGISTRY' ENTERED AT 11:26:43 ON 01 APR 2004

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 31 MAR 2004 HIGHEST RN 669692-30-2
DICTIONARY FILE UPDATES: 31 MAR 2004 HIGHEST RN 669692-30-2

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide can l18

L18 ANSWER 1 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 444990-66-3 REGISTRY
CN L-Alaninamide, N-acetyl-L-α-aspartyl-L-α-glutamyl-β-phenyl-L-phenylalanyl-L-α-glutamyl-3-cyclohexyl-N-[(1S)-1-(2,2-difluoroethyl)-3-methoxy-2,3-dioxopropyl]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
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SR CA
LC STN Files: CA, CAPLUS

RELATED SEQUENCES AVAILABLE WITH SEQLINK

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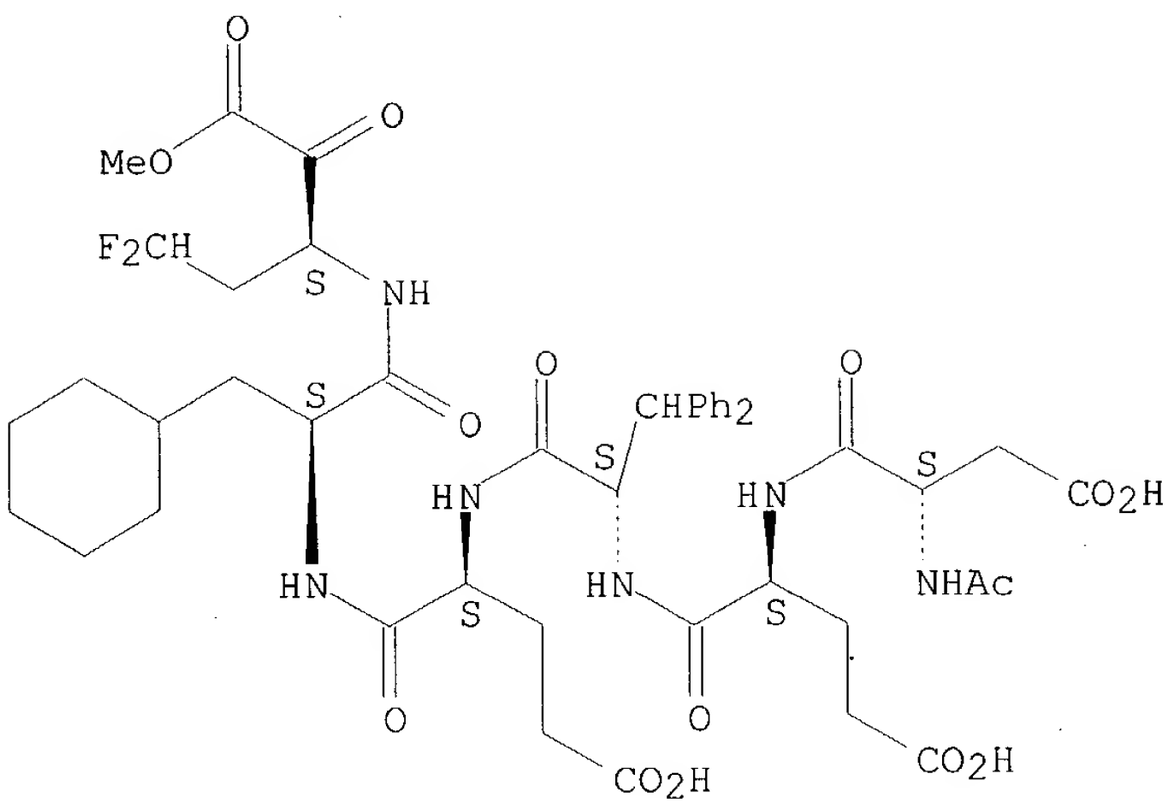

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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:149812

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L18 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 262437-57-0 REGISTRY
CN L-Alaninamide, N-acetyl-L-α-aspartyl-L-α-glutamyl-β-phenyl-L-phenylalanyl-L-α-glutamyl-N-[(1R)-1-(carboxycarbonyl)-3,3-difluoropropyl]-3-cyclohexyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C45 H56 F2 N6 O15
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

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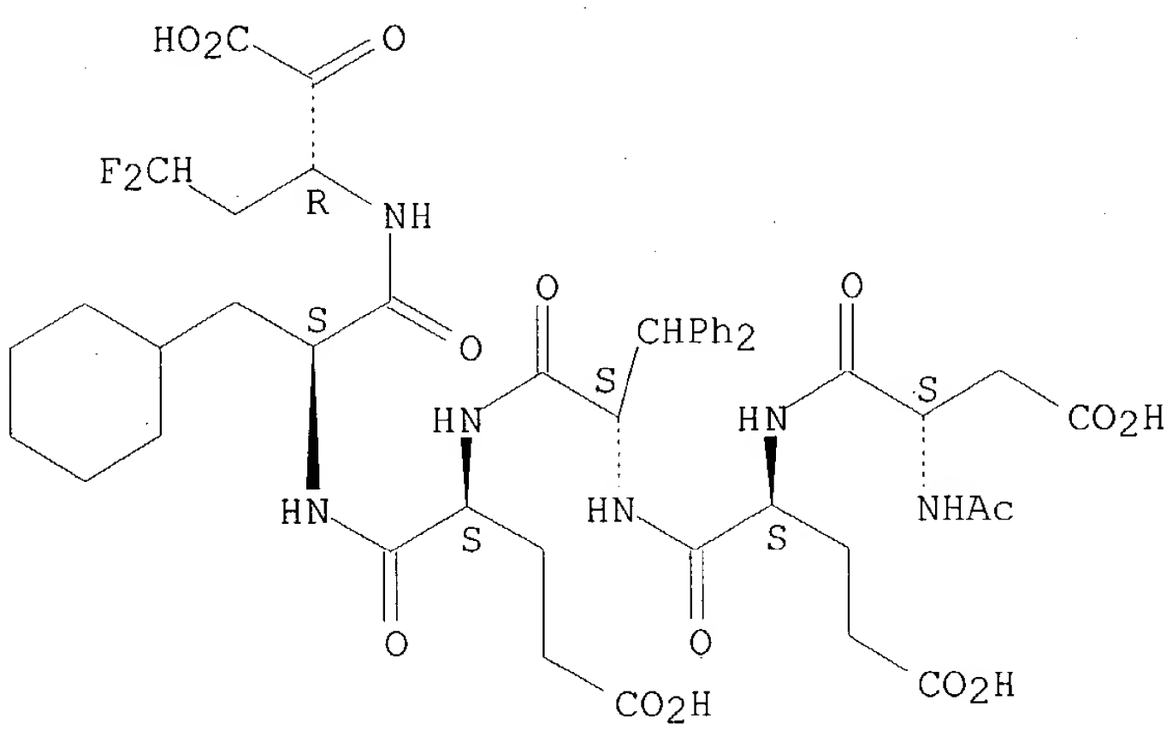
Absolute stereochemistry.



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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 132:245829

L18 ANSWER 3 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 262437-54-7 REGISTRY
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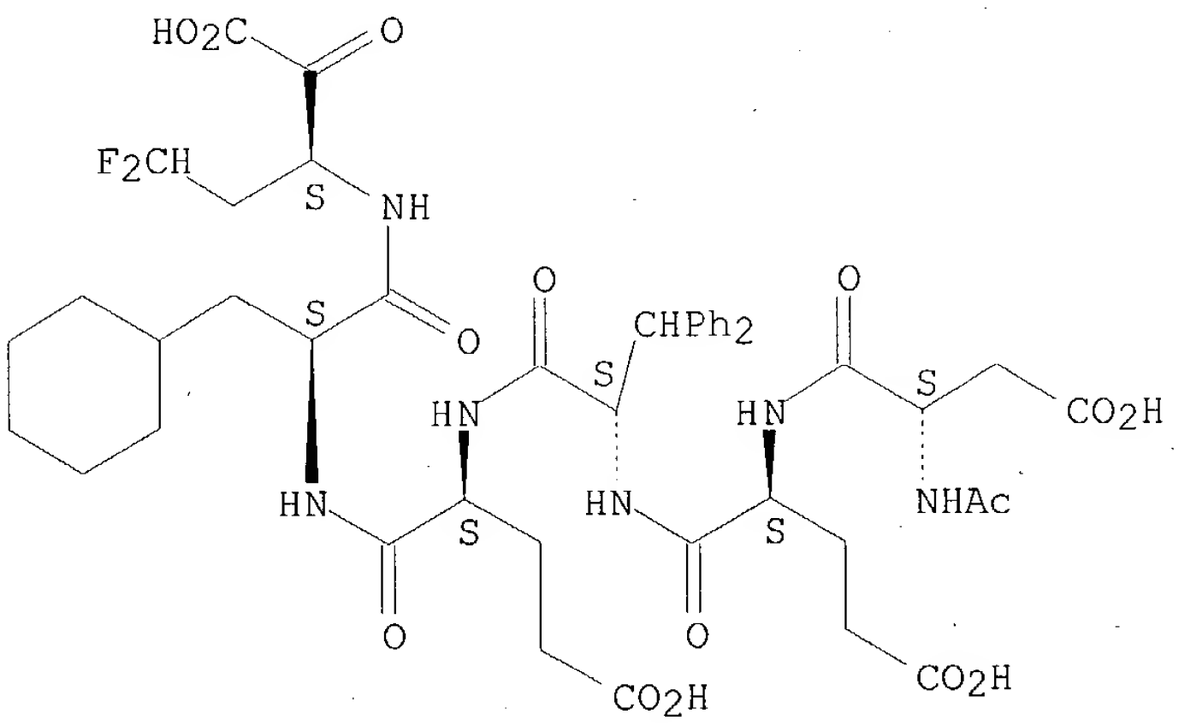
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C45 H56 F2 N6 O15
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.



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4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:149812

REFERENCE 2: 137:47425

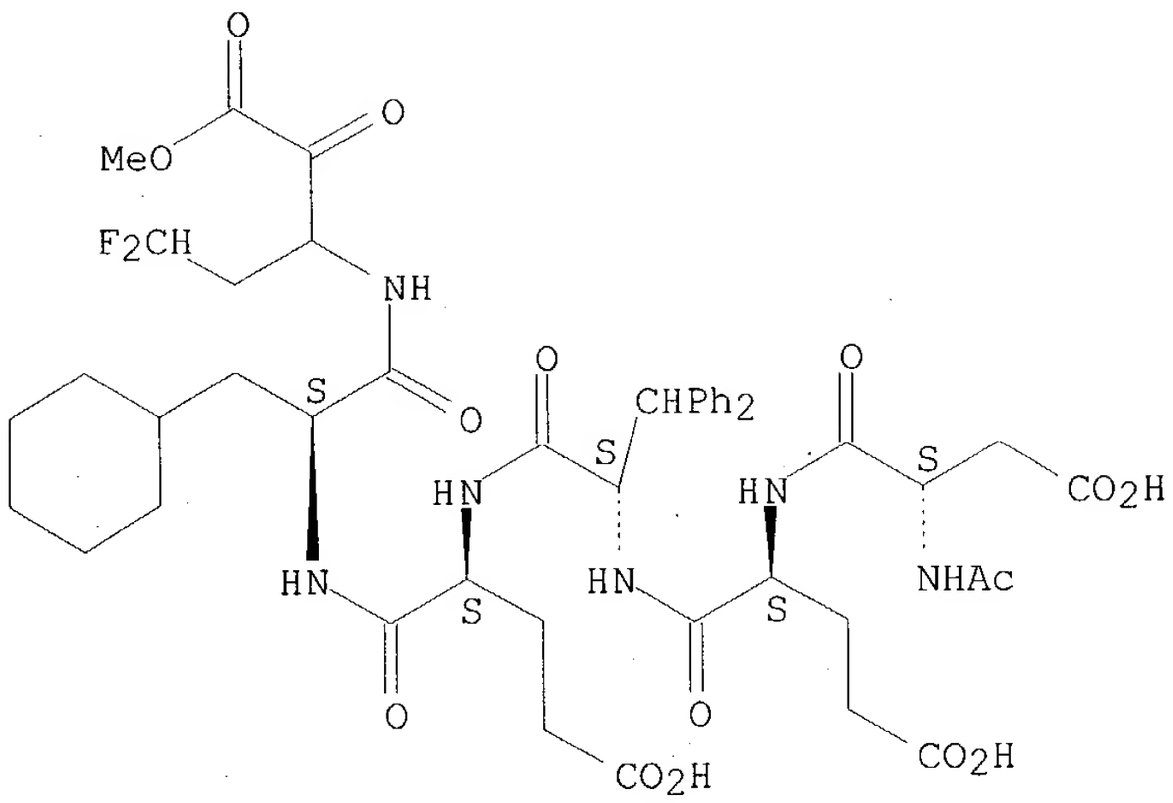
REFERENCE 3: 133:189820

REFERENCE 4: 132:245829

L18 ANSWER 4 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 252355-90-1 REGISTRY
CN L-Alaninamide, N-acetyl-L-α-aspartyl-L-α-glutamyl-β-phenyl-L-phenylalanyl-L-α-glutamyl-3-cyclohexyl-N-[1-(2,2-difluoroethyl)-3-methoxy-2,3-dioxopropyl]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C46 H58 F2 N6 O15
SR CA
LC STN Files: CA, CAPLUS

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.



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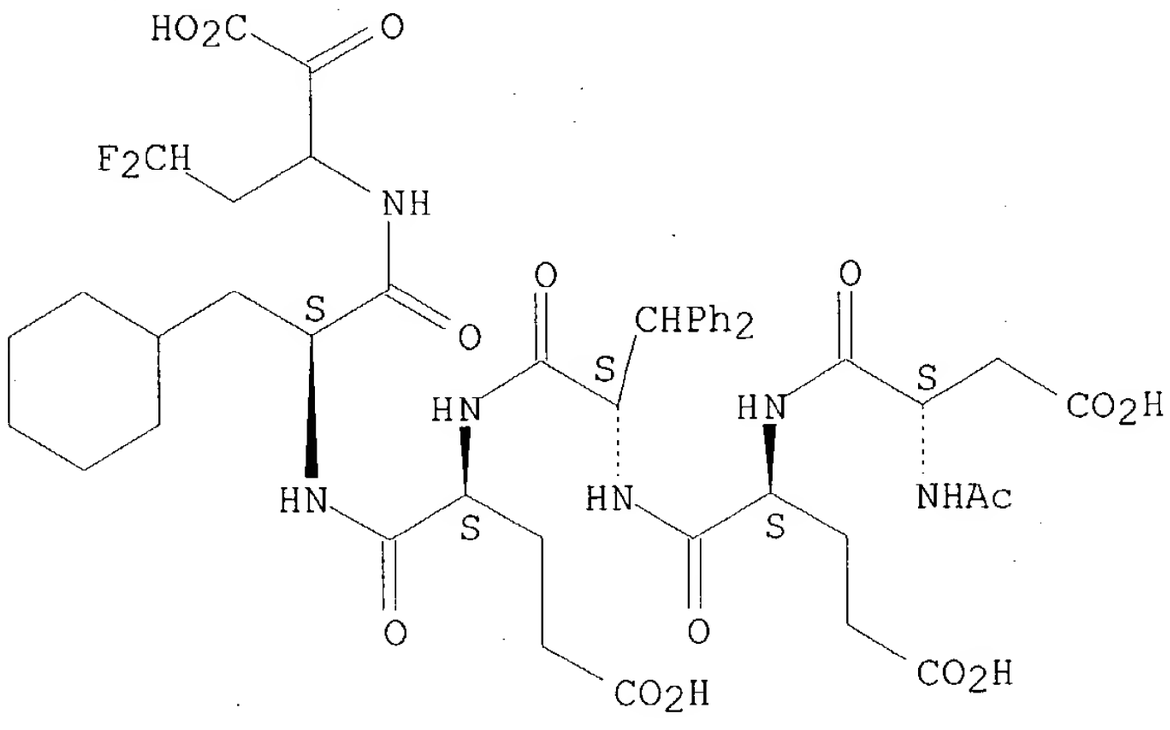
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 132:36034

L18 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 252355-88-7 REGISTRY
CN L-Alaninamide, N-acetyl-L-α-aspartyl-L-α-glutamyl-β-phenyl-L-phenylalanyl-L-α-glutamyl-N-[1-(carboxycarbonyl)-3,3-difluoropropyl]-3-cyclohexyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C45 H56 F2 N6 O15
SR CA
LC STN Files: CA, CAPLUS

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1907 TO DATE)
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REFERENCE 1: 132:36034